Study: NANT 2011-01

Randomized MIBG: ^{131}I-MIBG Alone vs. ^{131}I-MIBG with Vincristine and Irinotecan vs ^{131}I-MIBG with Vorinostat

Protocol Title: NANT 2011- 01: Randomized Phase II Pick the Winner Study of ^{131}I-MIBG, ^{131}I-MIBG with Vincristine and Irinotecan, or ^{131}I-MIBG with Vorinostat for Resistant/Relapsed Neuroblastoma.

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What is this study about?:

The purpose of this study is to compare three different treatments aimed at maintaining or improving response to previous treatments for neuroblastoma. This study involves the use of an investigational medicine called Metaiodobenzylguanidine (MIBG) alone and in combination with either Irinotecan and Vincristine or Vorinostat. All three MIBG treatment regimens have already been used for treatment of neuroblastoma and now we will compare their effects on tumor response and associated side effects. We are trying to see if in the end, one therapy is better for people with neuroblastoma.

Once patients are registered on this study, they will be randomly assigned to one of three treatments and will either receive ^{131}I-MIBG by itself or, ^{131}I-MIBG with Vincristine and Irinotecan, OR ^{131}I-MIBG WITH Vorinostat.

Random assignment means that the treatment to which a patient is assigned is based on chance. It is like a flip of a coin, and assignment is done by a computer. Neither patients nor their physicians will choose which treatment you will receive. All patients will have an equal chance of being placed in either treatment group. A total of 105 patients are expected to enroll on this study. There will be 35 patients on each arm. All patients will be assigned randomly. Patients on all treatment arms will receive stem cells as part of this therapy.

The three treatment arms are the following:

^{131}I-MIBG Alone:
MIBG is taken up by neuroblastoma tumor cells. MIBG can be combined together with radioactive iodine (^{131}I) in the laboratory to form the radioactive compound $^{131}I^{-}$MIBG. The $^{131}I^{-}$MIBG compound delivers radiation treatment to the neuroblastoma cancer cells throughout the body.

^{131}I-MIBG with Irinotecan and Vincristine:
This study will combine the two chemotherapy drugs, irinotecan and vincristine, that have been used together in some patients with neuroblastoma with the medicine called Metaiodobenzylguanidine (MIBG). The irinotecan / vincristine will be given at the same time as the $^{131}I^{-}$MIBG. Giving the chemotherapy together with the ^{131}I-MIBG may make the ^{131}I-MIBG more effective at treating neuroblastoma.

^{131}I-MIBG with Vorinostat:
Vorinostat is a drug that is FDA-approved to treat a certain type of cancer mainly seen in adults. Vorinostat affects the way the DNA that carries our genes is folded in cells. In the laboratory, vorinostat causes neuroblastoma cells to stop growing. This effect is even greater when vorinostat is combined with radiation. Giving vorinostat together with the ^{131}I-MIBG may make the ^{131}I-MIBG more effective at treating neuroblastoma.

Why is this study being done:

- To find out which of the three ^{131}I-MIBG therapies have a better tumor response rate after one treatment course.
- To compare the side effects seen by giving ^{131}I-MIBG alone, and ^{131}I-MIBG in combination with Vincristine and Irinotecan and ^{131}I-MIBG with Vorinostat
- To describe the describe which of the three ^{131}I-MIBG treatment regimens has the best tumor effect after two courses, including bone marrow, MIBG lesions, soft tissue lesions and overall survival.
- To describe how many patients who agree to send blood and bone marrow specimens for a special testing are found to have tumor cells by this new more sensitive test (called TLDA) after the each of the three ^{131}I-MIBG treatment regimens
- To compare the exposure of whole body radiation from ^{131}I-MIBG received on the three regimens using radiation measurements and blood markers of radiation.
- To learn about a new computerized way of reading MIBG scans.

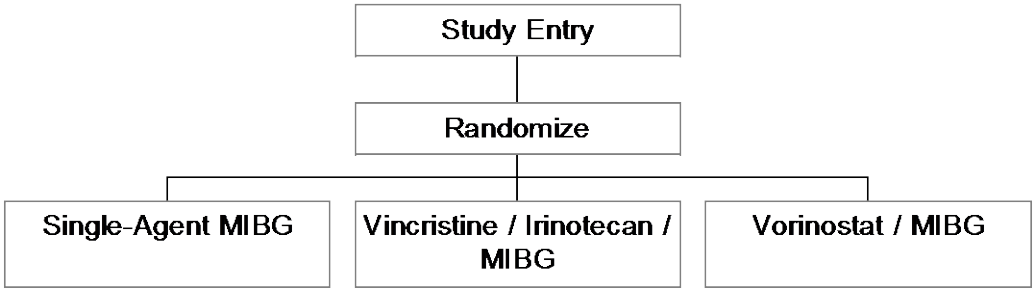
Criteria that need to be met to participate in this study:

- Patients must be $\geq$ 24 months and $\leq$ 30 years of age when registered on study.
- Patients must have relapsed neuroblastoma, refractory neuroblastoma that had less than a partial response to standard treatment or persistent neuroblastoma that had at least a partial response to frontline therapy frontline therapy with $\geq$ 3 residual lesions on end-induction MIBG scan.
- Patients must have evidence of MIBG uptake into tumor at ≥ one site within 3 weeks prior to entry on study and subsequent to any intervening therapy.
- Patients must have adequate heart, kidney, liver and bone marrow function. Patients who have bone marrow disease must still have adequate bone marrow function to enter the study.
- Patients must have a dose of unpurged peripheral blood stem cells is 2.0×10^6 viable CD34+ cells/kg available.

Patients cannot participate in the study if:

- They have other medical problems that could get much worse with this treatment.
- They are pregnant or breast feeding.
- They have a history of a venous or arterial thrombosis that was not associated to a central line.
- They have active infections such as hepatitis or fungal infections.
- They have active diarrhea.
- They have had an allogeneic stem cell transplant (received stem cell from someone else)
- They can't cooperate with the special precautions that are needed for this trial.

Study procedures:



All patients on this study will receive the same dose of ^{131}I-MIBG on Day -14 and autologous stem cell infusion on Day 0.

Patients can receive this therapy (each time on the same treatment arm) two times as part of this study, as long as:

--their tumor is not getting worse;

--they have not had any other anti-cancer treatments since the first course;

--they have enough stem cells to get a second course; and

--they have not had any bad side effects from the first course.

The second course cannot start earlier than Day 28 of the first course, as the ^{131}I-MIBG infusions must be at least 6 weeks apart.

A map of one treatment course on each treatment arm is shown below:

TREATMENT ARM A: ^{131}I-MIBG ALONE:

Days	1	15	43-50
Therapy	M	HSC	Eval

M = ^{131}I-MIBG
HSC = Stem cell infusion
Eval = Repeat disease evaluation

^{131}I-MIBG	**M**	**Day 1**
Stem Cell Infusion	**HSC**	**Day 15**
Evaluation	**Eval**	**Day 43-50**

TREATMENT ARM B: ^{131}I-MIBG + VINCRISTINE/IRINOTECAN:

Days	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**15**	**43-50**
Therapy	C	C V I	C I M	C I	C I	C I	C	C	HSC	Eval

C=Cefixime
M=^{131}I-MIBG
V=Vincristine
I=Irinotecan
HSC= Stem Cell Infusion
Eval=Repeat Disease Evaluation

Cefixime	**C**	**Days -1 through Day 6**
^{131}I-MIBG	**M**	**Day 1**
Irinotecan	**I**	**Days 0 through 4**
Vincristine	**V**	**Day 0**
Stem Cell Infusion	**HSC**	**Day 15**
Evaluation	**Eval**	**Day 43-50**

TREATMENT ARM C: ^{131}I-MIBG + Vorinostat

Days	-1	-0	1	2	3	4	5 - 12	15	43 -50
Therapy	**V**	**V**	**V** **M**	**V**	**V**	**V**	**V**	HSC	EVAL

M=^{131}I-MIBG
V= Vorinostat
HSC= Stem Cell Infusion
Eval= Repeat Disease Evaluation

Vorinostat	**V**	**Days –1 through 12 (total of 14 days)**
^{131}I-MIBG	**M**	**Day 1**
Stem Cells	**HSC**	**Day 15**
Evaluation	**Eval**	**43-50**

Information about Treatment with ^{131}I-MIBG

Treatment with ^{131}I-MIBG will be done at a hospital that is set up to take care of patients that are treated with radioactive substances. This means that patients may need to travel some distance to another hospital to get this treatment.

Patients will be admitted to a ^{131}I-MIBG treatment center one day before starting MIBG therapy. On the following day (Day 1), ^{131}I-MIBG is given into a temporary IV or in a central venous catheter over 90-120 minutes. IV fluids for hydration and other medicines will be given through central venous catheters.

Patients who get ^{131}I-MIBG are considered to be “hot” or radioactive and special precautions are taken to care for you during this time until the radiation level has gone down to a level where these precautions are no longer needed (usually 4 - 5 days). Special care precautions include:

- A single room in a bed surrounded by a lead shield to keep family and the staff who take care of you from being exposed to radiation from the ^{131}I-MIBG treatment. This usually takes about 5 days.
- The length of time family can visit inside the room in front of the protective lead shield that is around your bed will depend on how much radiation is measured in the room each day by the radiation specialist. Usually family can visit for a total of 30-45 minutes on the first day and longer on the days after that because there will be less radiation measured in the room each day.
- Family may visit anytime outside of the room behind a lead shield. You will be able to see who is visiting over this shield.
- No one will be able to spend the night in this special room with you during this time.
- A urinary catheter will be inserted through your urethra into the bladder to drain the radioactive urine from your body. This catheter will be removed 3 –5 days following the treatment.
- A medicine by mouth, (potassium iodide) will be needed to prevent thyroid damage from the radioactive iodine contained in the ^{131}I-MIBG compound. The medicine will be taken by mouth beginning before treatment and continuing for a total of 6 weeks.

Treatment with Vincristine and Irinotecan (Treatment Arm B only)

Patients randomized to **treatment arm B** will receive vincristine and irinotecan in addition to the ^{131}I-MIBG. All patients will get the same irinotecan and vincristine dose.

Before chemotherapy starts on this arm, patients will be given the antibiotic Cefixime (on Day -1) and will continue taking the Cefixime for a total of 8 days (until Day 6). Cefixime can be taken in tablet or liquid form. The purpose of the Cefixime is to reduce the chance of having bad diarrhea while getting the irinotecan. If there is trouble getting Cefixime, another antibiotic called cefpodixime can be used instead.
After one day of Cefixime, they will start taking irinotecan, vincristine and ^{131}I-MIBG. Irinotecan is given daily for 5 days in a row (Day 0 through 4) Irinotecan is given each day by IV over 1 hour. Vincristine is given by IV over 5 minutes only on the first day irinotecan is given (Day 0). Because the most common side effect of irinotecan is diarrhea, patients will also be instructed to take Loperamide (Imodium) after the first loose stool. The day after vincristine and the first dose of irinotecan are given; patients will be treated with ^{131}I-MIBG.

Treatment with Vorinostat (Treatment Arm C only)

Patients randomized to **treatment arm C** will receive vorinostat in addition to the ^{131}I-MIBG. All patients enrolled will get the same Vorinostat dose and receive vorinostat orally once daily on Days -1 through 12. Two days after starting Vorinostat, ^{131}I-MIBG will be given (Day 1).